Functional analyses of sphingolipid biosynthesis in an apicomplexan parasite

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Abstract

The phylum Apicomplexa includes many parasites that cause serious human and animal disease, for example *Plasmodium* (malaria), *Eimeria* (coccidiosis) and *Toxoplasma* (toxoplasmosis). Treatments against these parasites are limited and novel solutions are urgently required. Recently, research has focused on parasite specific features of lipid biosynthesis as potential drug targets. In particular the biosynthesis of sphingolipids, which have essential roles in many processes, has been highlighted as a potential target.

Using the model apicomplexan *Toxoplasma gondii* we are studying the role of parasite and host sphingolipid biosynthesis in invasion and proliferation. To do this we are functionally characterizing the *Toxoplasma* sphingolipid biosynthetic pathway. In parallel, the response of the host sphingolipid biosynthetic pathway to parasite infection is being investigated. Results so far demonstrate that host cell SPT is up-regulated on *T. gondii* infection, indicating that sphingolipid biosynthesis is increased. However, metabolic labelling shows that several distinct complex sphingolipids, including inositol phosphorylceramide (IPC), are synthesized independently by the parasite. The fungal IPC synthase inhibitor aureobasidin A (AbA) has been reported to target *Toxoplasma* IPC synthesis. Our results show that AbA and an orthologue are active against the parasite, however their effect on *Toxoplasma de novo* sphingolipid biosynthesis is unclear.

Together these approaches will lead to further understanding of the roles of sphingolipid biosynthesis in parasitism and also demonstrate the possibilities of targeting the parasite pathway for therapeutic intervention.